

AD-A037 978

OHIO STATE UNIV COLUMBUS DEPT OF AERONAUTICAL AND AS--ETC F/G 6/19  
CARDIOVASCULAR, RENAL AND RESPIRATORY EFFECTS OF HIGH INTENSITY--ETC(U)  
JUL 76 R M NEREM, R L HAMLIN, G M PANTALOS AF-AFOSR-2526-73

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AFOSR - TR - 77 - 0319

RF Project 3656-A1  
Report No. 3

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43212

CARDIOVASCULAR, RENAL AND RESPIRATORY EFFECTS OF HIGH  
INTENSITY, INTERMEDIATE DURATION, LOW  
FREQUENCY VIBRATION

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1 July 1975 - 30 June 1976

DEPARTMENT OF THE AIR FORCE  
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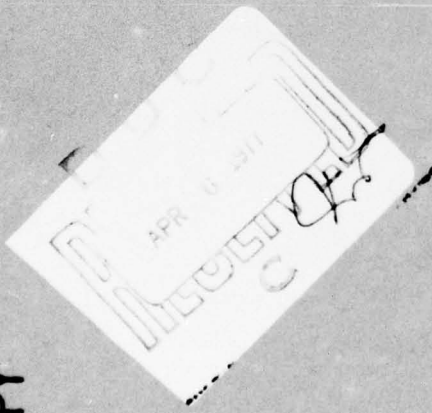
Grant No. AFOSR-73-2526

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19 REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER AFOSR - TR - 77 - 0319	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) CARDIOVASCULAR, RENAL AND RESPIRATORY EFFECTS OF HIGH INTENSITY, INTERMEDIATE DURATION, LOW FREQUENCY VIBRATION.	5. TYPE OF REPORT & PERIOD COVERED Interim <i>rept. no. 3</i> 1 Jul 1975 - 30 June 1976	6. RF Project 3656-A1; Rep. #3
7. AUTHOR(s) Robert M. Nerem Robert L. Hamlin George M. Pantalos	8. CONTRACT OR GRANT NUMBER(s) 15 - AF - AFOSR - 78-2526-73	
9. PERFORMING ORGANIZATION NAME AND ADDRESS The Ohio State University Research Foundation Department of Aero and Astro Engineering 1314 Kinnear Road, Columbus, Ohio 43212	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 61102F/9777-02/	
11. CONTROLLING OFFICE NAME AND ADDRESS Air Force Office of Scientific Research (NL) 1400 Wilson Boulevard Arlington, Virginia 22209	12. REPORT DATE 31 Jul 1976	
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office) 12 22p.	13. NUMBER OF PAGES 21	
	15. SECURITY CLASS. (of this report) Unclassified	
	15a. DECLASSIFICATION/DOWNGRADING SCHEDULE	
16. DISTRIBUTION STATEMENT (of this Report) Approved for public release; distribution unlimited.		
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)		
18. SUPPLEMENTARY NOTES		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number) Wholebody vibration; cardiovascular; albumin and cholesterol transport; arterial and regional blood flow measurements		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) A research program on the influence of high intensity, intermediate duration, low-frequency wholebody vibration on the cardiovascular, renal and respiratory systems is described. During the period 1 July 1975 to 30 June 1976, emphasis was placed on the <u>in vitro</u> study of the transport of $^{14}\text{C}$ -4-cholesterol between blood and the arterial wall in the presence of oscillatory flow conditions. In addition, a previous <u>in vivo</u> investigation of $^{131}\text{I}$ -albumin transport in the aorta was extended to include measurements during vibration at 6 and 14 Hz. These <u>in vivo</u> studies indicate an enhancement of albumin uptake during vibration in the		



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dog aorta. The in vivo data are consistent with in vitro data and the concept of a shear-dependent transport process. Continuing in vivo studies are being carried out to measure aortic pressure and velocity waveforms. Considerable progress has been made in the use of radioactive microspheres in regional blood flow studies and in developing a pulsed ultrasonic doppler velocimeter for non-invasive flow measurements.

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## I. INTRODUCTION

The research effort described herein is being conducted with the support of AFOSR Grant No. 73-2526 entitled "Cardiovascular, Renal and Respiratory Effects of High Intensity, Intermediate Duration, Low Frequency Vibration." The emphasis to date has been on the influence of wholebody vibration on blood-arterial wall transport. It is felt that the results obtained are significant in that they demonstrate an important influence of vibration on the transport of materials between blood and the arterial wall. These are the first measurements to demonstrate an effect of vibration on such a basic aspect of wall physiology. In the next few sections, a brief review will be presented of progress made since the inception of this Grant on June 1, 1973, and in particular, during the last twelve months.

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## II. IN VIVO MEASUREMENTS OF BLOOD-ARTERIAL WALL <sup>131</sup>I-ALBUMIN TRANSPORT

The primary emphasis of the experiments carried out to date has been to study the influence of wholebody vibration on the transport of albumin between blood and the arterial wall. In vivo measurements of <sup>131</sup>I-albumin uptake in the canine aorta have been carried out for control conditions and during wholebody vibration at frequencies of 6, 10, and 14 Hz with a peak-to-peak amplitude of 1.27 cm. The results obtained in the posterior ascending aorta are summarized in Figure 1. Shown on the ordinate of Figure 1 is the uptake or wall permeability parameter,  $\dot{m}/C_0$ , where  $\dot{m}$  is the measured uptake of albumin per unit area per unit time (i.e., g/cm<sup>2</sup>-s) and  $C_0$  is the concentration of labelled albumin in the blood; i.e., g/cm<sup>3</sup>. Thus  $\dot{m}/C_0$  is the characteristic velocity of the blood-arterial wall uptake process in cm/s. In Figure 1 the abscissa is the parameter  $C.O.^{3/2}/D^{7/2}$ , where C.O. is cardiac output and D is the ascending aorta diameter. This parameter is directly related to the mean shear rate, S, at the wall of the ascending aorta, and it has been shown that the use of this parameter leads to a better correlation of the results from control experiments. It should also be noted that the mean aortic wall shear stress,  $\tau_w$ , is equal to  $\mu S$  where  $\mu$  is the viscosity coefficient. For the conditions of this study, the mean wall shear stress ranges from 2 to 10 dyn/cm<sup>2</sup>.

From Figure 1, it appears that the uptake of albumin by the aortic wall shows a mild to moderate dependence on the wall shear parameter. There is a definite enhancement of uptake at lower mean shear parameter values for all vibration frequencies. These curve fits to the data also suggest that, regardless of the magnitude of the uptake, the dependence on the wall shear parameter decreases with an increase in frequency. At present, no explanation can be offered for the inverse dependence of uptake on shear at 6 Hz. Although the data do show definite shear-dependent trends, the statistical significance must be questioned because of the large standard mean deviation which ranges from 16.8 to 30.7 percent.

The spatial distribution of albumin uptake along the aorta has also been examined. The averaged values from the nine sampling sites on the aorta (see Figure 2) are listed for each set of experiments in Table I. It appears that for the control experiments, the level of uptake at the sites along the aorta is similar to, if not greater than, the uptake at the posterior ascending aorta position. However, in the vibration experiments, the level of uptake was found to decrease as one progressed down the aorta from the posterior ascending aorta position. One consistent pattern found in both control and vibration experiments was that for the non-branched regions of the aortic arch, posterior samples had greater averaged levels of uptake than the anterior samples. In terms of a shear-dependent uptake process, this is consistent with a higher level of shear on the inside wall of a curved pipe in the presence of entry flow.

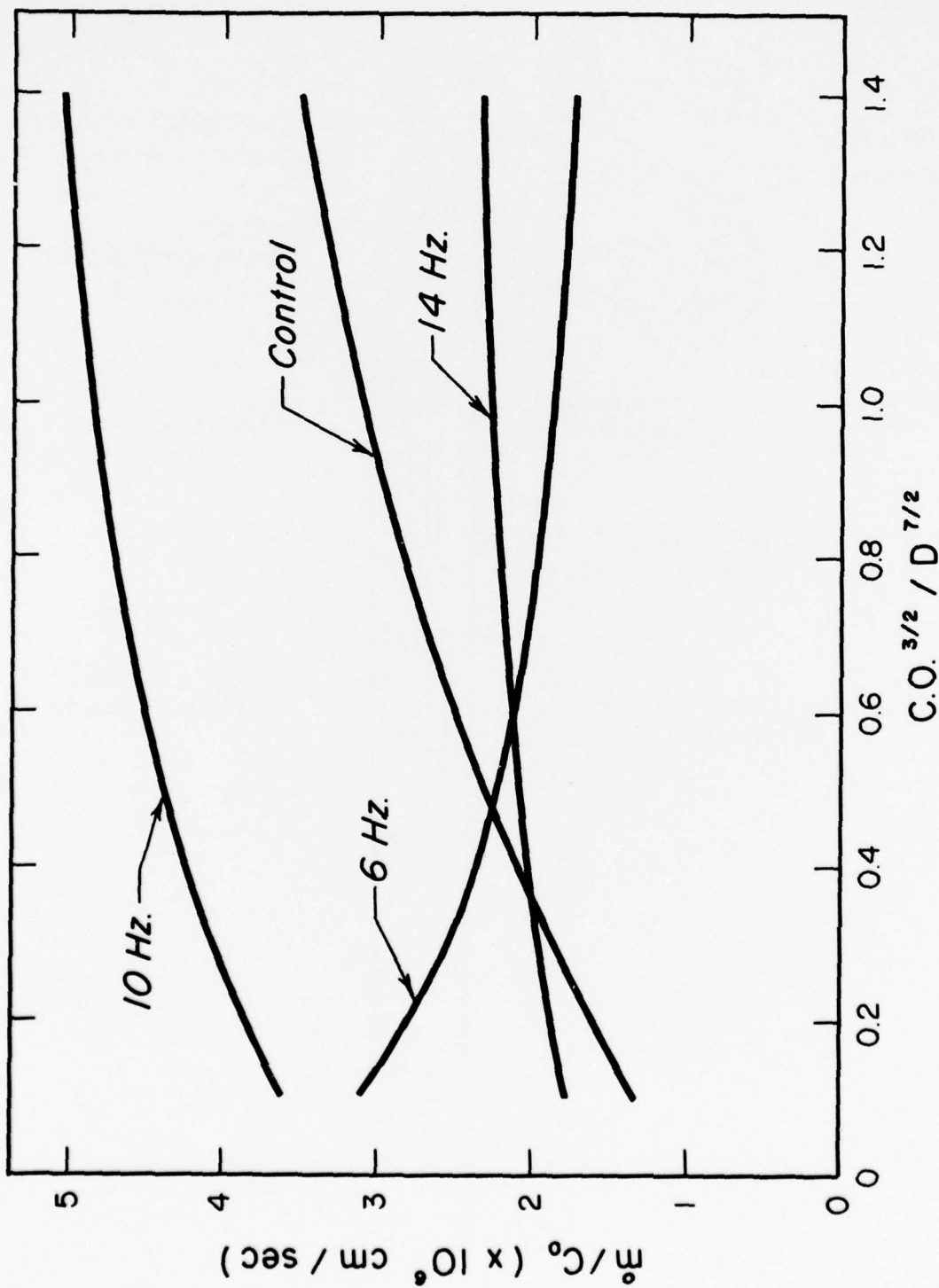


Figure 1. Least squares curve fit of measured uptake of  $^{131}\text{I}$ -albumin in the posterior ascending aorta as a function of wall shear parameter,  $\text{C.O.}^{3/2} / \text{D}^{7/2}$ , for control and vibration conditions at 6, 10, and 14 Hz.

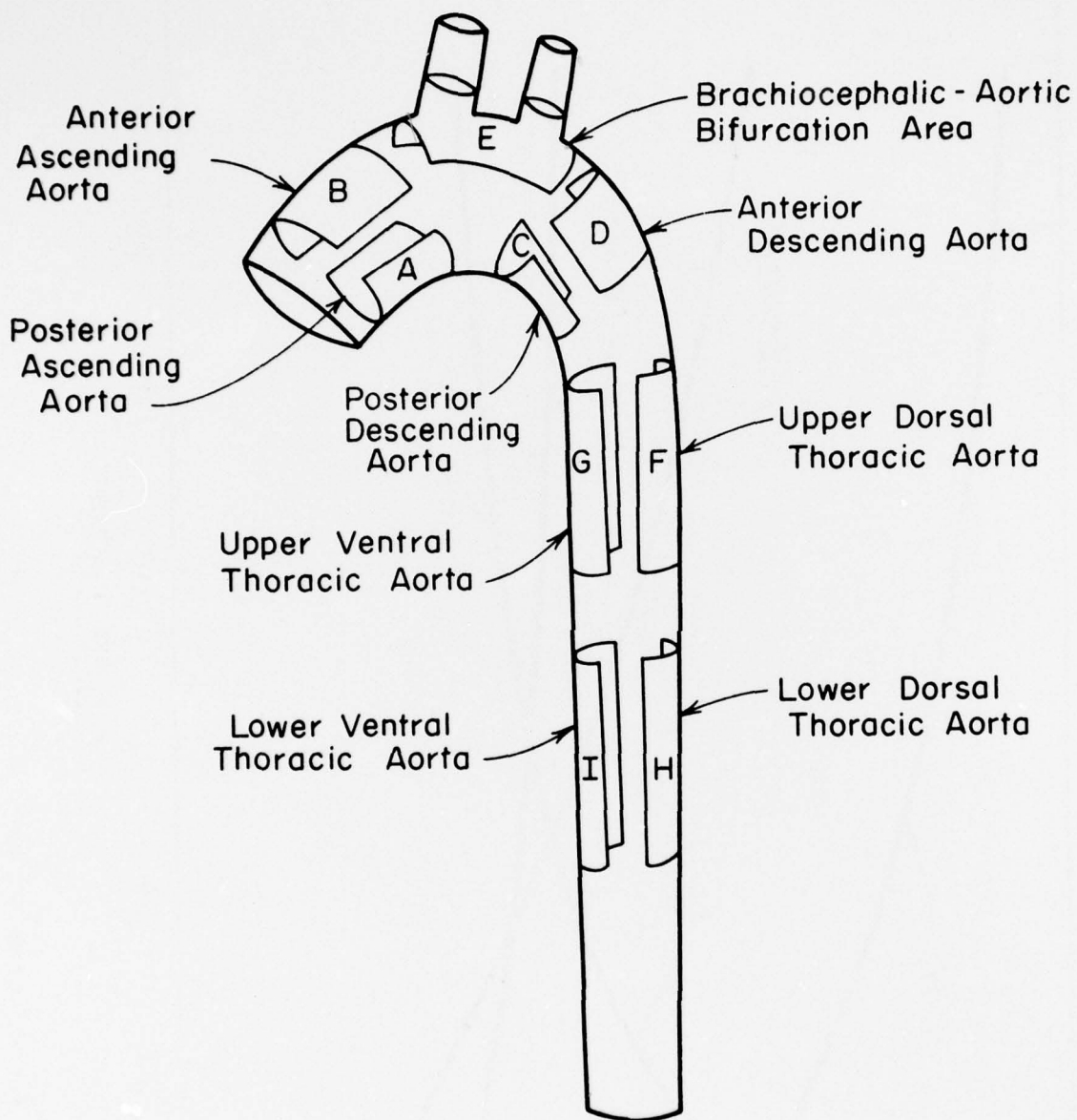


Figure 2. Aortic sampling sites for  $^{131}\text{I}$ -albumin uptake studies.



Table I. Distribution of Averaged Uptakes  
Along the Aorta (Normalized to Posterior Ascending Aorta)

Frequency (Hz)	A	B	C	D	E	F	G	H	I
0	1.00	0.76	1.05	0.97	1.32	1.56	1.11	1.46	0.93
6	1.00	1.11	0.92	0.88	1.12	0.76	0.79	0.72	0.65
10	1.00	0.70	0.88	0.62	0.83	0.76	0.61	0.68	0.68
14	1.00	0.82	0.82	0.90	0.96	0.83	0.70	0.73	0.68

### III. IN VITRO MEASUREMENTS OF BLOOD-ARTERIAL WALL <sup>14</sup>C-4-CHOLESTEROL TRANSPORT

During the third year of effort on this grant, considerable emphasis has been placed on the in vitro study of blood-arterial wall <sup>14</sup>C-4-cholesterol transport for oscillatory flow conditions. The results of these experiments are quite similar to those obtained for <sup>131</sup>I-albumin and indicate, in general, enhanced uptake with increasing wall shear stress. In fact, it may be of importance when considering the mechanism of transport that two grossly different molecules (i.e., albumin and cholesterol) have virtually the same level of uptake for similar flow conditions and have the same dependence on wall shear stress (see Figure 3).

The oscillatory flow experiments, which have been limited in frequency to up to 4 Hz, lend further support to any conclusion about the rate-limiting mechanism since, in the limit of diffusion boundary layer control, no shear dependence would be expected. However, the data obtained do demonstrate a shear-dependence. These results thus suggest, not only that the transendothelial transport of albumin and cholesterol is controlled by a fluid-wall interface process, but that it is one which has a frequency response that is relatively flat up to 4 Hz. Furthermore, the wholebody vibration results are consistent with our earlier hypothesis which includes the idea of vibration-induced flow changes and a shear-dependent transport process. To this extent, then, the in vivo and in vitro results support one another.

Finally, a comparison of the magnitude of uptake in the in vivo and in vitro cases indicates that these are compatible if the pulsatile nature of the in vivo flow is considered. As an example, for the ascending aorta where the mean shear stress is approximately 10 dyn/cm<sup>2</sup> for the present anesthetized animal experiments,  $\dot{m}/C_0$  is on the order of 2 to 4 x 10<sup>-6</sup> cm/s. In the steady-state in vitro perfusion experiments and for a wall shear stress of 10 dyn/cm<sup>2</sup>,  $\dot{m}/C_0$  is no more than 4 x 10<sup>-7</sup> cm/s. Even accounting for the fact that in vivo there will be albumin transport from the outside of the vessel and in through the vasa vasorum, the in vivo uptake is still higher by a factor of three than the corresponding in vitro uptake for the same mean wall shear stress. However, the peak shear stress in vivo may be on the order of 100 dyn/cm<sup>2</sup> and for such a stress level, even under oscillatory conditions,  $\dot{m}/C_0$  values in excess of 10<sup>-6</sup> cm/s are not unrealistic.

Whether this is purely a flow effect or whether pressure pulsations also play a role cannot be decided at this time. However, the transport of albumin or cholesterol between blood and the arterial wall does appear to be controlled by a shear-dependent transendothelial process. This process is sensitive to low-frequency pulsations of the order of 1-4 Hz and in vivo the pulsatile components of the flow may actually dominate over the mean flow in controlling the uptake phenomena.

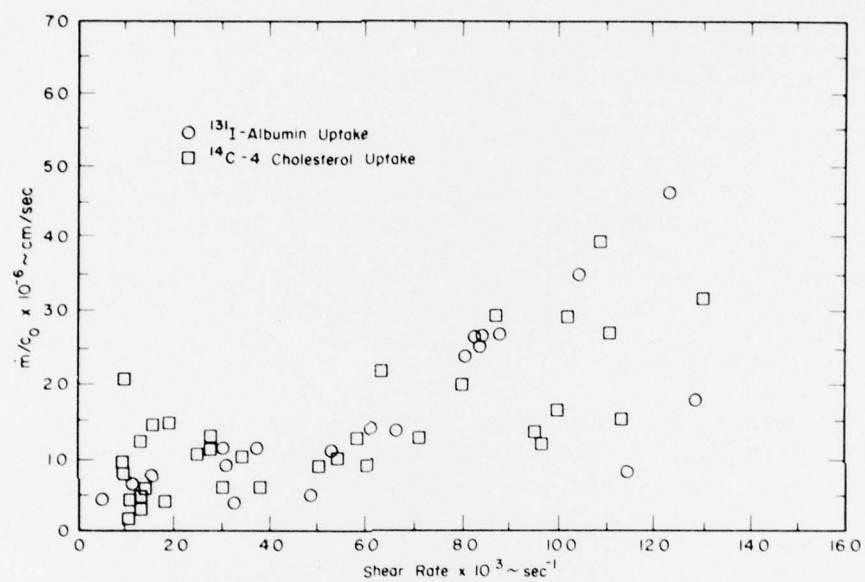


Figure 3. In vitro arterial uptake of  $^{131}\text{I}$ -albumin and  $^{14}\text{C}$ -4-cholesterol in the presence of oscillatory flow conditions.



#### IV. AORTIC PRESSURE AND VELOCITY MEASUREMENTS

In addition to the albumin and cholesterol uptake studies, exploratory in vivo hot-film anemometer velocity and pressure waveform measurements have been continued using a catheter tip probe in the aorta of anesthetized dogs undergoing longitudinal vibration. The purpose of these measurements is to determine the character of blood flow in presence of wholebody vibration and to monitor transient changes in aortic flow. Aorta velocity measurements have been carried out for both nonvibration and vibration conditions in the ascending and descending aorta at 6 and 10 Hz. These measurements were performed using a catheter hot-film probe mounted in a Pieper umbrella gage which has expandable sides such that the probe is positioned in the center of the aorta.

In these studies, large changes in the shape of the velocity waveform have been observed with an induced velocity component due to vibration being present which affects different portions of the velocity waveform differently, depending upon the time during the cardiac cycle. The large change in the peak centerline velocity caused by vibration cannot be explained. However, velocity measurements made several minutes after the cessation of vibration have indicated peak velocities of the same magnitude as during vibration, but which differed slightly in the shape of the basic waveform.

Using these results, the shear stress at the aorta wall, caused by the vibration-induced sinusoidal velocity component, has been calculated. In the ascending aorta at both 6 and 10 Hz, an average half-amplitude velocity component of 3 cm/s was measured, resulting in an estimated increase in peak wall shear stress of about 4 dyn/cm<sup>2</sup>. However, in the descending aorta, an average half-amplitude velocity component of 6 cm/s was measured at both frequencies. This results in an estimated increase in peak wall shear stress of approximately 8 dyn/cm<sup>2</sup>. These values are somewhat less than previously reported.

These results can also be used to estimate a transmission factor. This is done by ratioing the induced blood flow velocity to the vibration velocity of the table or carriage to which the animal is attached. For a frequency of 10 Hz and a half-amplitude of 0.535 cm, the vibration velocity is approximately 40 cm/s. Compared to the induced blood flow velocity of 3 to 6 cm/s, this suggests a transmission factor of approximately 13 to 26 percent.

It should be mentioned that the difficulties in obtaining reliable centerline velocity data primarily were due to deployment failure of the Pieper umbrella. Often the umbrella became fouled by contact with the vessel wall and would not open fully. Hence, the probe was not held firmly in the center of the aorta, but was free to move during vibration. This made it difficult to determine which portion of the change in velocity waveform was due to changes in velocity as a result of vibration and which portion was due to vibration of the probe.

To remedy this problem, in recent experiments probes have been inserted in the femoral artery of animals and as close to the iliac bifurcation as possible. In addition, the exposed femoral arteries have been doused with xylocaine several minutes prior to probe insertion. Xylocaine is a vasodilator, hence, the enlarged artery makes insertion of the probe easier and this has greatly reduced the incidence of probe fouling.

With these difficulties hopefully overcome, the studies now are being continued to investigate the possible presence of flow turbulence during wholebody vibration. Whether or not turbulent ascending aortic flow occurs depends on cardiac output and heart rate. Since both of these are influenced by vibration, it will be of interest to determine whether the influence of wholebody vibration is to drive the flow toward a more unstable or turbulent condition or in the opposite direction.

Pressure waveform measurements have also been made in the ascending and descending aorta of dogs exposed to 4, 6, 8, and 10 Hz vibration. The modification of the pressure waveform during vibration appears to be primarily the superposition of an oscillating pressure pattern on the normal waveform. These pressure oscillations have a peak amplitude of 3 to 5 mm Hg. However, it has not been possible to establish marked differences in pressure fluctuations between ascending and descending aortic positions.

## V. REGIONAL BLOOD FLOW MEASUREMENTS

Measurements of regional blood flow have been carried out in animals for control and 10 Hz vibration conditions. The motivation for these experiments was the need to understand whether albumin uptake by the aortic wall is primarily transendothelial in nature or due to blood perfusion via the vasa vasorum. Since, as noted previously, albumin uptake by the aortic wall is influenced by wholebody vibration, the answer to the question above has significance in terms of whether the vibration effect is largely one associated with aortic flow changes or one associated with microcirculation changes.

The regional flow measurements were made by injection of a measured activity of radiolabeled microspheres, 15  $\mu$ m in diameter, into the left ventricle during control and vibration conditions. The percent of microspheres retrieved from each tissue sample (determined by counting emissions in a deep-well scintillation counter) was used to determine the percent of cardiac output which traversed the tissue sample. Samples from the aorta, like those taken in the albumin uptake experiments, were analyzed as well as tissue samples from the heart, kidney, liver, spleen, testes, epididymus, pampiniform plexus, skin, and skeletal muscle.

The data from the regional blood flow experiments suggest that, with vibration, there is little change in the rate of perfusion in the arch region of the aorta. However, there is a marked increase in blood perfusion rate to the descending aorta and to several of the organs sampled. The ratios of perfusion rate for vibration to control conditions are presented in Figure 4. Although the data do suggest certain trends, it is still necessary to establish a statistically valid basis for these trends. If the current data, when subjected to more rigorous statistical analysis, do not show any statistical significance, further experiments will be required.

If the suggested trends in perfusion rate modification do prove to have some level of significance, it is interesting to speculate on the relationship between change in regional blood flow rate and albumin uptake with vibration. As previously noted, it appears that regional blood flow rates increase in the descending aorta with vibration, while showing little change in the aortic arch region. Comparison of data from the control and 10 Hz albumin uptake experiments indicates vibration-enhanced uptake in the arch region of the aorta and decreased uptake in the descending aorta.

The ratio of uptake to blood perfusion rate during vibration divided by the uptake to perfusion rate during control conditions is noted in Figure 5. These data again suggest that vibration enhances uptake in the arch region of the aorta while enhancing regional blood flow in the descending aorta. These results also seem to support the concept that the effect of vibration on uptake is mostly associated with aortic flow modification rather than microcirculation flow changes. From a system functioning point of view, it suggests that enhanced uptake occurs in the



<u>Sample</u>	<u>Ratio</u>
A	1.17
B	1.24
C	0.98
D	1.15
E	1.00
F	1.49
G	1.69
H	1.61
I	1.56
Heart	1.28
Kidney	1.38
Liver	0.82
Spleen	1.30
Musc.	1.42
Skin	0.88
Testes	1.33
EPI	1.58
PP	2.44



Figure 4. Ratio of regional blood flow rate for vibration and control conditions.

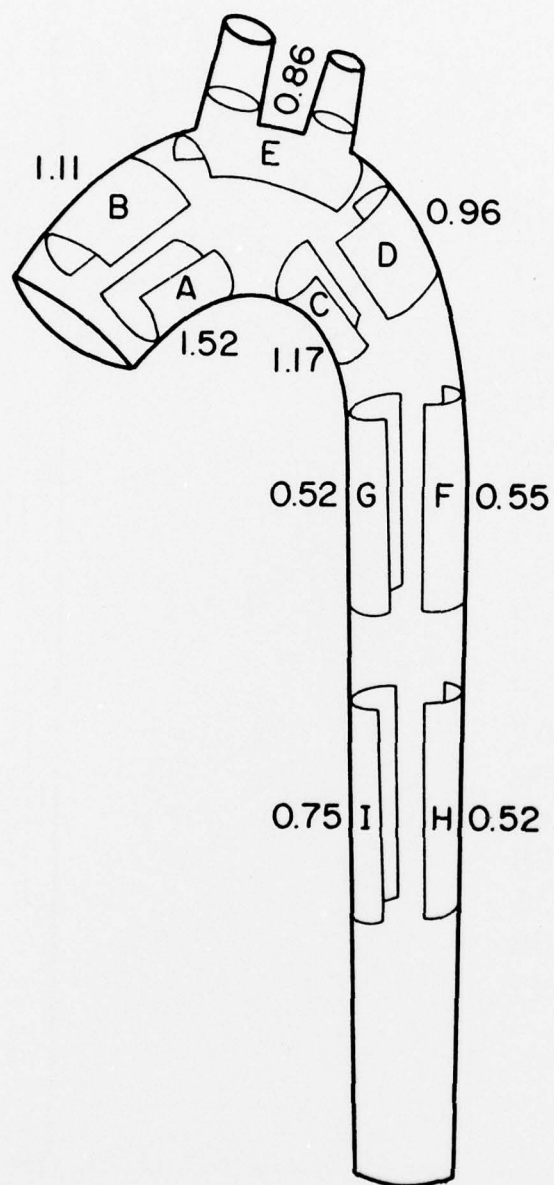


Figure 5. Ratio of regional albumin uptake and blood flow rate for vibration and control conditions.

region of the aorta that is relatively normal to the vibration, while increased regional blood flow occurs in the region of the aorta that is parallel to the vibration. This, however, is subject to further experimental verification.

## VI. PULSED ULTRASONIC DOPPLER VELOCIMETER DEVELOPMENT

Although we have been successful in obtaining flow data from hot-film anemometry apparatus, the desire for a non-invasive flow measurement capability has led to the initiation of the development of a pulsed ultrasonic doppler velocimeter. It is intended that the velocimeter will be used in various cardiovascular flow studies including those involving acceleration environments.

To date, the pulsed ultrasonic doppler system has been designed and is currently being constructed. Initial performance tests are expected to begin within the next month. It should be emphasized that the doppler system under development is a pulsed, rather than a continuous wave (CW), doppler system. The use of a pulsed system will give much greater spatial resolution in the flow to be measured than a CW system. Initially the system will operate at 12 MHz, but will eventually be upgraded to function at 20 MHz. It is anticipated that the high frequency of operation will enable accurate profiles of the flow to be obtained and will offer the possibility of detecting flow turbulence.



## VII. CONCLUDING DISCUSSION

The in vivo and in vitro results presented here are consistent with an interpretation based on shear-dependent mass transport and with our earlier hypotheses (Arch. Environ. Health 26:105, 1973). The  $^{131}\text{I}$ -albumin and  $^{14}\text{C}$ -4-cholesterol results suggest that macromolecule transport between blood and the arterial wall is controlled by a shear-dependent interfacial process with a frequency response which is flat up to at least 4 Hz. Estimates of the enhancement of wall shear stress during wholebody vibration have been carried out using measurements of the aortic pressure and velocity waveforms obtained during wholebody vibration and these calculations also support the interpretation of uptake enhancement as being due to vibration-induced shear stresses coupling with a shear-dependent mass transport process. Combined results from in vivo albumin uptake studies and regional blood flow studies suggest that vibration enhances the mass transport process in the arch region of the aorta while increasing blood flow to the microcirculation in the descending aorta. These observations also indicate that the effect of vibration on uptake is primarily due to aortic flow modification rather than microcirculation flow changes.

In order to extend the basis of these tentative conclusions and to further test their validity, the following specific areas are now under investigation:

Additional in vivo studies with cholesterol, will be completed during the present grant period. In addition, an in vitro study of the influence of pressure and flow pulsations on cholesterol transendothelial transport will be conducted.

Secondly, simultaneous with the completion of these studies, our effort is undergoing a shift of emphasis to the problem of blood flow measurement, particularly as it relates to cardiovascular behavior in an acceleration environment. Obviously, wholebody vibration represents such an acceleration environment and exploratory studies of this type in dogs using a hot-film, constant-temperature anemometer were described in the preceding section. These studies are now being continued in an attempt to better map out the extent of vibration-induced blood flow changes; e.g., its nature--is it laminar or is it disturbed or even turbulent, the shape of the velocity waveform, and peak velocities, accelerations, and flow Reynolds numbers.

An additional aspect to this proposed shift in emphasis to the problem of blood flow measurement is that of the development of the instrumentation itself. The research group here has an extensive background in the application of constant temperature hot-film anemometry to blood velocity measurements. Even so, there are questions which logically present themselves and which must be answered in terms of the further application of hot-film devices. An example of this is the use of a hot-film catheter probe to make measurements in man and the extension of our present studies to pilots under various stress situations. To supplement current hot-film

anemometer studies and to provide for the development of a non-invasive flow measurement capability, a pulsed doppler ultrasonic velocimeter is being constructed and is expected to be fully operational in the next year. This pulsed doppler system should enable the measurement of blood flow in many situations that do not lend themselves to measurement by hot-film anemometers and will hopefully improve the accuracy of the flow data.

## APPENDIX

### PUBLICATIONS AND PRESENTATIONS

The following presentations and publications of results obtained from research sponsored by AFOSR Grant 73-2526 have either been made or are under preparation:

1. Nerem, R. M.; Pantalos, G. M.; and Schwerin, W. D., "Influence of High Intensity, Low Frequency Vibration on the Transport of Albumin Between Blood and the Arterial Wall," presented at the Review of Air Force Sponsored Basic Research in Environmental and Acceleration Physiology, held October 24-26, 1973 at the USAF Academy, Colorado.
2. Schwerin, W. D., "Effects of Low Frequency, High Intensity, Wholebody Vibration on the Uptake of  $^{131}\text{I}$ -Albumin in the Canine Aorta," M.Sc. Thesis, The Ohio State University, 1974.
3. Nerem, R. M.; Hamlin, R. L.; Schwerin, W. D., "Cardiovascular, Renal and Respiratory Effects of High Intensity, Intermediate Duration, Low Frequency Vibration," Annual Report on AFOSR Grant No. 73-2526, July 18, 1974.
4. Nerem, R. M., and Hamlin, R. L., "Influence of High Intensity, Low Frequency Vibration on the Cardiovascular System," presented at the Review of Air Force Sponsored Basic Research in Environmental and Acceleration Physiology, held October 8-10, 1974 at Brooks Air Force Base, Texas.
5. Nerem, R. M.; Mosberg, A. T.; and Schwerin, W. D., "Transendothelial Transport of  $^{131}\text{I}$ -Albumin," presented at the Second International Congress on Biorheology, The Weizmann Institute of Science, Rehovot, Israel, December 29, 1974-January 7, 1975; accepted for publication in Biorheology.
6. Nerem, R. M., and Schwerin, W. D., "Influence of Wholebody Vibration on  $^{131}\text{I}$ -Albumin Uptake by the Canine Aorta," presented at the 59th Annual Meeting of the Federation of American Societies for Experimental Biology, Atlantic City, April 13-18, 1975.
7. Nerem, R. M.; Pantalos, G. M.; and Schwerin, W. D., "Influence of Wholebody Vibration on  $^{131}\text{I}$ -Albumin Uptake by the Canine Aorta," journal article in preparation.
8. Nerem, R. M.; Pantalos, G. M.; and Schwerin, W. D., "Blood-Arterial Wall Transport of  $^{131}\text{I}$ -Albumin in the Presence of Wholebody Vibration," presented at the 28th Annual Conference on Engineering in Medicine and Biology, New Orleans, Louisiana, September 22-25, 1975.

9. Nerem, R. M., "Vibration Enhancement of Blood-Arterial Wall Macromolecule Transport," presented at the NIOSH-FAO/ECE/ILO Symposium on medical, physiological, epidemiological, psychological, and engineering aspects of occupational hand-arm vibration, Cincinnati, Ohio, October 28-30, 1975.
10. Pantalos, G. M., "Fluid Mechanical Effects in the Cardiovascular System Due to Vibrational Stresses Experienced in Spaceflight," to be presented at the National Student Conference, Annual Meeting of the American Institute of Aeronautics and Astronautics, January 11-13, 1977, Washington, D. C.